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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,815	06/06/2002	Takehiko Koide	06478.1461	2579

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 05/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/018,815	Applicant(s) KOIDE, TAKEHIKO	
	Examiner Malgorzata A. Walicka	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 and 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The examiner acknowledges the application, which is a 371 application of the PCT/JP00/04101 application. Claim 1-6 are pending and are the subject of this Office Action.

DETAILED ACTION

1. Priority

Acknowledgment is made of Applicants' claim for priority based on an application filed in Japan on 06/23/99.

2. Objections

The sentence on page 1, line 8 is not grammatical; correction is necessary.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

3. Rejections

3.1. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.1.1. Lack of written description

Claim 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a human antithrombin variant characterized in that at least one of the amino acids at positions 78, 278, 378 and 380 are changed. The claims are directed to a large genus of human thrombin variants, but the specification fails to describe its structure. No single representative species of the genus is disclosed by presenting its amino acid sequence and its sequence identification number; neither the encoding gene of the polypeptide is given. Therefore, one skilled does not know what amino acid sequence is to be modified so that its amino acids in positions 78, 278, 378 and 380 are substituted.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. The written description requirement is satisfied by the disclosure of

the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem.* 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as structures, or figures presenting such structures or even words presenting details of structures claimed. Because the specification completely lacks the amino acid and nucleotide sequence that are to be mutated to obtained the claimed invention, one skilled in the relevant art concludes that the inventor(s), at the time the application was filed, had no possession of the claimed invention.

3.2.2. Lack of enablement

Claim 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a human antithrombin variant characterized in that at least one of the amino acids at positions 78, 278, 378 and 380 are changed. The specification, however, fails to teach the amino acid and DNA structures that are to be mutated. Therefore, to make and use the claimed invention undue experimentation is necessary.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any variant of human antitrombin wherein amino acid in positions 78, 278, 378 and 380 are changed. However, the specification fails to disclose a single amino acid and/or DNA sequence of any human ant thrombin variant; see the above rejection for lack of written description. Thus, one skilled in the art is forced to change codons encoding any human thrombin from natural or man-made source, wherein said codons are coding amino acid residues 78, 278, 378 and 380. Such modification do not necessary lead to the variant of desired characteristic, i.e. heparin independent, because the starting DNA, and amino acid sequences include all possible variants of antithrombin III and other antithrombins. Thus, although the knowledge of mechanism of thrombin inhibition and antithrombin III properties are well developed, and skills of artisan high, the experimentation necessary to make the claimed invention has a low probability of success.

Without further guidance on the part of Applicants as to the sequence of the human antithrombin to be modified in positions 78, 278, 378 and 380, experimentation left to those skilled in the art is improperly extensive and undue.

3.3. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Huntington J. A. et al. (Conformational Conversion of Antithrombin to a Fully Activated Substrate of Factor Xa without Need for Heparin, *Biochemistry* 1998, 37, 3272-3277); copy enclosed.

The claims are directed to a human antithrombin, and encoding DNA, characterized in that the amino acids at positions 380 is substituted.

Huntington et al. generated, by site directed mutagenesis, a variant of antithrombin wherein serine in position 380 is substituted by cysteine. The variant does not require heparin activation for its inhibitory function.

3.4. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huntington J. A. et al. (Mechanism of Heparin Activation of Antithrombin. Evidence for Reactive Center Loop Preinsertion with Expultion upon Heparin Binding, *Biochemistry*, 1996, 35, 8495-8503, and Conformational Conversion of Antithrombin to a Fully Activated Substrate of Factor Xa without Need for Heparin, *Biochemistry* 1998, 37, 3272-3277); copies of both articles enclosed, in view of common knowledge in molecular biology.

Huntington et al. generated, by site directed mutagenesis, a variant of antithrombin wherein serine in position 380 is substituted by thryptophan (1996) or cysteine (1998); see the abstracts of both papers. The variants do not require heparin activation for its inhibitory function. Huntington et al. do not teach substitution of residue 380 by alanine, aspartic acid, glycine, histidine, ileucine, lecine, asparagines, threonine, tyrosine, and valine.

It would have been obvious to one having ordinary skill in the art at the time of invention to have antithrombin and modify it to heparin independence by substituting the residue 380 by amino acid other than tryptophan and cysteine.

The motivation is provided by Huntington et al. who write, "This accounts both for the occurrence of thrombosis in patients whose antithrombin has a defect in heparin binding or activation and for the widespread clinical use of exogenous heparin as anticoagulant" (page 3272 of the 1998 paper, left column, line 20). Thus, one skilled in the art would be motivated to obtain antithrombin that is more clinically useful by making it independent on its activator, heparin. The expectation of success was very high, because Huntington et al. teach that position 380, having functional symbol P14, needs to be displaced from beta-sheet A of the protein to render it heparin independent (page 3272 of 1998 paper, right column, line 33.). The displacement can be achieved by substitution of serine 380 by other amino acid.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

5. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number

is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600